

ODE Argument for Dispute Resolution Panel, Sept 6

The primary endpoint in the pivotal clinical study for Intergel® Adhesion Prevention Solution was an intent-to-treat analysis of the the modified American Fertility Society (mAFS) score, which measures the presence, extent and severity of adhesions on a scale of 0-16. The study was designed to evaluate whether Intergel reduced the mAFS score by 2.1 compared to the control, lactated Ringer's solution. The result was a reduction in mAFS score of 0.13 for Intergel using the ITT analysis and a 0.97 reduction in mAFS score for Intergel using the evaluable patient population. The sponsor reports a 45% reduction in mAFS score for Intergel compared to control, which is derived from the evaluable analysis in which the mAFS score for Intergel was 1.21 and control was 2.18. The General and Plastic Surgery Devices Panel (GPS Panel) met and made recommendations on January 12, 2000. The GPS Panel recommended and the Office of Device Evaluation (ODE) concurs that the PMA be considered not approvable because the results of the pivotal clinical study did not demonstrate reasonable assurance of safety and effectiveness under the conditions of use prescribed [515(d)(2)(B)]. It is the opinion of ODE and the panel that the data did not show a clinically significant benefit for the Intergel® Solution-treated group when compared to the lactated Ringer's solution control group. Additionally, the patients in the treatment group exhibited a small, but numerically higher overall infection rate than that observed for the control patients. The increase in infection, though numerically small, may be of clinical significance due to the multifactorial nature of clinical problems such as infertility that may affect this patient population.

The sponsor provided additional materials in Amendment 11 (received June 2, 2000), which were intended to address the concerns voiced by ODE and the GPS Panel, were not new data, but retrospective reanalyses of the data presented to the GPS Panel at the January 12, 2000 panel meeting. These reanalyses used the observations designed to obtain a Modified AFS score to assess a more restricted endpoint – consideration of adnexal adhesions - by reconstructing an AFS score. There is little experience in the clinical literature correlating the mAFS score with clinical outcome. When the data are then reorganized into a different scale for later analysis, correlation of the results to any clinically meaningful outcome becomes difficult. The AFS score data and the associated "shift tables" had been presented to the GPS Panel in a slightly different form at the January 12, 2000 meeting. This analysis examined the proportions of patients with no adhesions, minimal/mild adhesions and moderate/severe adhesions at baseline and at second look in the Intergel® Solution and Control groups. This analysis reported a statistical benefit that was driven by the baseline moderate/severe patients, accounting for approximately 10% of the study population. However, these moderate/severe patients were not the patients the original study was designed and powered to evaluate. Also, the original study was not powered and designed for a standard AFS score analysis. When one performs an intent-to-treat analysis (proscribed in the original protocol), there was no difference between groups at second look for the patients who had no or minimal/mild adhesions at baseline (these groups included the vast majority of the study patients). Infections were reanalyzed in several ways, but in all analyses the infection rate for Intergel was numerically small, but higher than the control.